

# Guillain-Barré Syndrome Following Influenza Vaccination

Penina Haber, MPH

Frank DeStefano, MD, MPH

Fredrick J. Angulo, DVM, PhD

John Iskander, MD, MPH

Sean V. Shadomy, DVM, MPH

Eric Weintraub, MPH

Robert T. Chen, MD, MA

**G**UILLAIN-BARRÉ SYNDROME (GBS) is an acute, immune-mediated paralytic disorder of the peripheral nervous system.<sup>1</sup> Concerns about the risk of developing GBS following influenza vaccination have been present since an association was first noticed during the 1976-1977 A/New Jersey ("swine influenza") season.<sup>2</sup> A statistically significant elevated risk of GBS was found in swine flu vaccinees relative to non-vaccinees within 6 to 8 weeks after vaccination.<sup>3-7</sup> Evidence for a relationship between GBS and other influenza vaccines, however, is less clear.<sup>8</sup> After 1977, most studies of GBS and influenza vaccines found low relative risks that were not statistically significant.<sup>9-12</sup> A study of the 1992-1993 and 1993-1994 seasons found a combined relative risk for GBS among influenza vaccine recipients of 1.7 (95% confidence interval, 1.0-2.8;  $P = .04$ ) during the 6 weeks following vaccination.<sup>13</sup>

Because the antigenic composition of influenza vaccine varies from year to year and the potential for risk of GBS also varies, we have been monitoring trends in reports of GBS to the Vaccine Adverse Event Reporting System (VAERS) following influenza vaccination since the system's inception in 1990.<sup>14-17</sup> Herein we report our analysis of those trends.

**Context** An unexplained increase in the risk of Guillain-Barré syndrome (GBS) occurred among recipients of the swine influenza vaccine in 1976-1977. Guillain-Barré syndrome remains the most frequent neurological condition reported after influenza vaccination to the Vaccine Adverse Events Reporting System (VAERS) since its inception in 1990.

**Objective** To evaluate trends of reports to VAERS of GBS following influenza vaccination in adults.

**Design, Setting, and Participants** VAERS is the US national spontaneous reporting system for adverse events following vaccination. Reports of GBS in persons 18 years or older following influenza vaccination were evaluated for each influenza season from July 1, 1990, through June 30, 2003. The number of people vaccinated was estimated from the National Health Interview Survey and US census data. Beginning in 1994, active follow-up was conducted to verify GBS diagnosis and obtain other clinical details.

**Main Outcome Measure** Reporting rates of GBS following influenza vaccination over time.

**Results** From July 1990 through June 2003, VAERS received 501 reports of GBS following influenza vaccination in adults. The median onset interval (13 days) was longer than that of non-GBS reports of adverse events after influenza vaccine (1 day) ( $P < .001$ ). The annual reporting rate decreased 4-fold from a high of 0.17 per 100 000 vaccinees in 1993-1994 to 0.04 in 2002-2003 ( $P < .001$ ). A GBS diagnosis was confirmed in 82% of reports. Preceding illness within 4 weeks of vaccination was identified in 24% of reported cases.

**Conclusions** From 1990 to 2003, VAERS reporting rates of GBS after influenza vaccination decreased. The long onset interval and low prevalence of other preexisting illnesses are consistent with a possible causal association between GBS and influenza vaccine. These findings require additional research, which can lead to a fuller understanding of the causes of GBS and its possible relationship with influenza vaccine.

JAMA. 2004;292:2478-2481

www.jama.com

## METHODS

VAERS is a national postmarketing spontaneous reporting system for vaccine adverse events following receipt of US-licensed vaccines.<sup>14-17</sup> We selected all VAERS reports of GBS following influenza vaccination in persons at least 18 years old who were vaccinated between July 1990 and June 2003.

To estimate the proportion of the population receiving influenza vaccination by age and season, we used data from the National Health Interview Survey.<sup>18</sup> Census estimates of the popula-

tion<sup>19</sup> by age group were multiplied by the proportion of people receiving influenza vaccine in the same age groups to determine the number of people vac-

**Author Affiliations:** National Immunization Program, Centers for Disease Control and Prevention (Ms Haber, Drs DeStefano, Iskander, Shadomy, and Chen, and Mr Weintraub); and National Center for Infectious Diseases, Division of Bacterial and Mycotic Diseases (Dr Angulo), Atlanta, Ga.

**Corresponding Author:** Penina Haber, MPH, Immunization Safety Branch, Epidemiology and Surveillance Division, National Immunization Program, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, Mail Stop E-61, Atlanta, GA 30333 (PHaber@cdc.gov).

cinated. We calculated age-specific reporting rates by dividing the number of VAERS reports of GBS following influenza vaccination by the estimated number of people who received influenza vaccine in each age group and season. We compared reporting rates of GBS following influenza vaccination with all other non-GBS adverse event reports by influenza season and onset interval, where influenza season was defined as July 1 through June 30 and onset interval as the number of days from the vaccination date to the date of reported symptom onset.

We performed Poisson regression analyses for linear trend to assess reporting trends with adjustments for age and sex, as appropriate, for all GBS reports and for those that were verified on follow-up. Statistical analysis was performed with the PROC GENMOD module in SAS version 8.2 (SAS Institute Inc, Cary, NC). Statistical significance was set a priori as  $P < .05$ .

During each influenza season since 1994, we conducted active follow-up of all GBS reports following influenza vaccination to verify the diagnosis and to obtain additional clinical information (eg, prior illness within 4 weeks before onset of GBS, history of prior influenza vaccination, and prior GBS occurrence).

To determine how the trends in GBS reporting to VAERS compare with GBS trends in the general population, we analyzed hospital discharge data from the Nationwide Inpatient Sample.<sup>20</sup> We analyzed GBS primary hospital discharge diagnoses (*International Classification of Diseases, Ninth Revision* code 357.00) and used annual census data of the population of participating states to calculate annual GBS hospital discharge rates.

## RESULTS

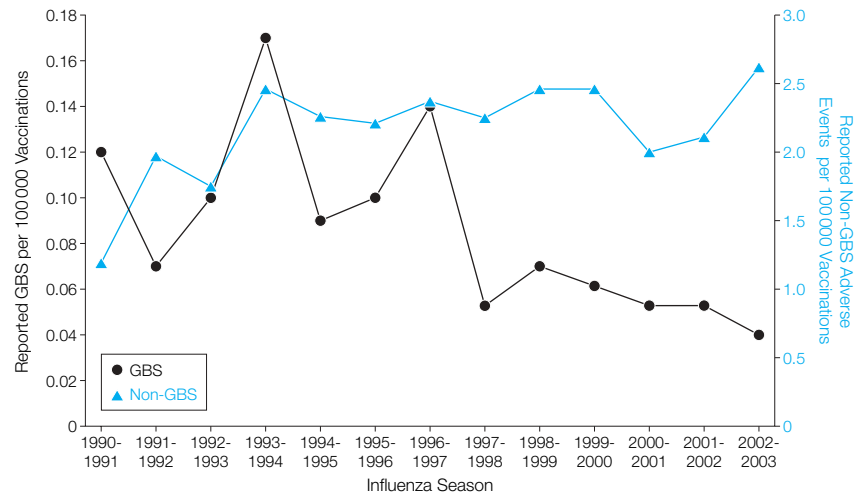
From July 1990 through June 2003, VAERS received 501 reports of GBS following influenza vaccination in persons at least 18 years old. Annual reporting rates of GBS per 100 000 influenza vaccinations declined ( $P < .001$ ) from a high of 0.17 in 1993-1994 to a low of 0.04 in 2002-2003

(FIGURE 1). In contrast, there was a significant ( $P < .001$ ) increase in the reporting rates of non-GBS adverse events after influenza vaccination. Reporting rates of GBS decreased in all age groups

(FIGURE 2 and TABLE), whereas age group-specific trends varied for the non-GBS reports (Table).

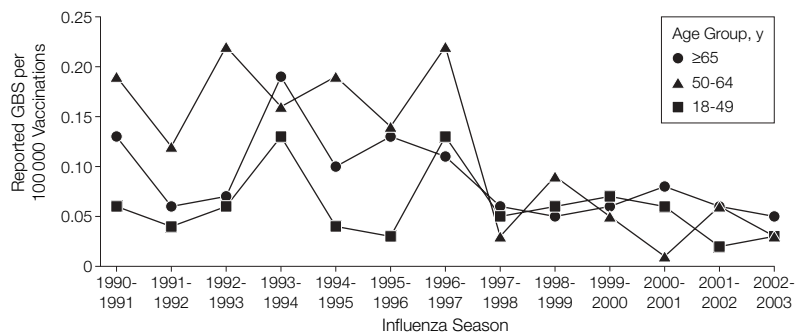
Reports of GBS had a different pattern of onset intervals from non-GBS

**Figure 1.** Rates of GBS and Non-GBS Reports Following Influenza Vaccination, VAERS 1990-2003



GBS indicates Guillain-Barré syndrome; VAERS, Vaccine Adverse Events Reporting System.

**Figure 2.** Reporting Rates of GBS by Age and Influenza Season, VAERS 1990-2003



GBS indicates Guillain-Barré syndrome; VAERS, Vaccine Adverse Events Reporting System.

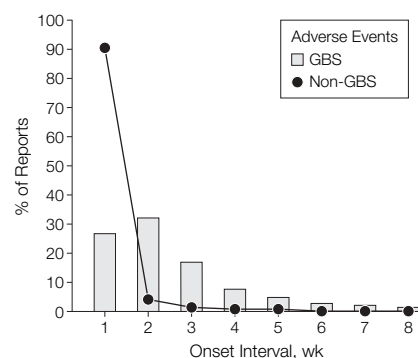
**Table.** Temporal Trends in Guillain-Barré Syndrome (GBS) and Non-GBS Adverse Event Reporting Rates Following Influenza Vaccination, VAERS 1990-2003

	Age Group, y			
	18-49	50-64	≥65	All Ages
GBS				
Coefficient*	-0.0734	-0.1565	-0.0812	-0.0977
P value	.004	<.001	<.001	<.001
Non-GBS				
Coefficient*	0.0168	0.0072	-0.0114	0.0142
P value	<.001	.21	.005	<.001

Abbreviation: VAERS, Vaccine Adverse Events Reporting System.

\*Estimated annual change in reporting rate per 100 000 persons vaccinated.

**Figure 3.** Onset Interval of Symptoms of GBS and Non-GBS Adverse Events Following Influenza Vaccination, VAERS 1990-2003



GBS indicates Guillain-Barré syndrome; VAERS, Vaccine Adverse Events Reporting System. Data for weeks 6 through 8 following vaccination are 0.2% for non-GBS reports.

reports, with the median onset interval for GBS reports (13 days) being longer than that of non-GBS reports after influenza vaccination (1 day) (range, 0-741 days) ( $P < .001$ ). Fifty-nine percent of all GBS reports for which the onset interval was available (286/486) noted symptom onset within 0 to 14 days following vaccination, while 94.5% of all non-GBS reports noted symptom onset within the same time interval (FIGURE 3).

In the GBS follow-up study during 1994 through 2003, we obtained information for 323 GBS reports. We excluded reports for persons lost to follow-up ( $n=33$ ) and those with a non-GBS diagnosis ( $n=26$ ) and analyzed the remaining 264 confirmed GBS reports (82%). The trend was similar to all GBS reports. The follow-up study also found that a preceding illness within 4 weeks of vaccination was present in 24% of reported cases ( $n=76$ ), and 105 had received influenza vaccine in the previous seasons.

In the analysis of hospital discharge trends for GBS using Nationwide Inpatient Sample data, we found that from 1989 to 1997 discharge rates were relatively unchanged, fluctuating around 3.2 per 100 000 population ( $P = .11$ ). From 1997 through 2001, however, the hospital discharge rate for GBS de-

creased from 3.1 to 2.5 per 100 000 population ( $P = .009$ ).

## COMMENT

Since the inception of VAERS in 1990, we have observed extensive variability in reporting rates of GBS after influenza vaccination but most notably a marked decline since the 1996-1997 season. This pattern was not observed with non-GBS reports. Possible explanations for these findings include changes in vaccine coverage, reporting artifacts, general decline in GBS overall, or changes in the influenza vaccine that could be causally related to GBS.

Influenza vaccination coverage in adults increased 2-fold from 1988-1989 to 1999-2000 among healthy adults and high-risk persons older than 18 years.<sup>21</sup> If younger people who are at decreased risk for GBS were being vaccinated, it could have resulted in decreased reporting rates of GBS after influenza vaccination. This is not a likely explanation for our findings, however, since we found decreases in GBS reporting rates in all age groups and we adjusted the annual rates for age.

Like all passive surveillance systems, VAERS is subject to underreporting, differential reporting, and variability in report quality and completeness.<sup>22</sup> Reporting to VAERS is more likely when the adverse event is severe or occurs shortly after vaccination, the vaccine is newly introduced, and when there has been publicity about a vaccine adverse event.<sup>16,17,23,24</sup> We tried to address concerns about the quality of the VAERS data by performing a follow-up study in which we were able to confirm a diagnosis of GBS in 82% of the reports, and analyses restricted to confirmed reports did not alter our findings. We also found similar results in a subanalysis restricted to cases with onset less than 6 weeks following vaccination and thus more likely to have been causally related to vaccination. We do not think that diminishing awareness of GBS following influenza vaccination is a likely explanation of our findings because a major study that found an increased risk of GBS following influenza vaccination

was published in 1998.<sup>13</sup> Moreover, reporting of non-GBS adverse events after influenza vaccination did not decrease over time.

At least 2 of our findings suggest that many of the reports to VAERS of GBS following influenza vaccination were not entirely coincidental. First, the reported onset interval differed for GBS reports compared with other influenza vaccine VAERS reports (Figure 3). Second, the relatively low prevalence of antecedent illness in our study (24%) was similar to the findings of the swine flu investigations (33% in vaccinated cases compared with 62% in unvaccinated cases). During the swine flu investigations, the markedly lower proportion of vaccinated compared with unvaccinated cases with a history of a recent illness provided strong evidence for a causal relationship between influenza vaccination and GBS, suggesting that vaccine replaced acute illness as a trigger of GBS.<sup>2</sup>

The significant decrease in GBS hospital discharges in the general population from 1997 through 2001 in the Nationwide Inpatient Sample suggests that the decrease in GBS reports to VAERS may be due at least in part to a general decline in the background rate of GBS. This is unlikely to be the only explanation since the decline in GBS reports to VAERS following influenza vaccination after 1996 (60%) was much steeper than the corresponding decline in Nationwide Inpatient Sample GBS hospital discharge rates (20%). However, both of these decreases may be related.

Influenza vaccines have traditionally been made in chicken eggs, and *Campylobacter* is an endemic infection among chickens and a known cause of GBS.<sup>25,26</sup> The Food-borne Diseases Active Surveillance Network (FoodNet) has found that from 1996 to 2003, laboratory-confirmed *Campylobacter* infections in humans decreased 28% in the United States due to enhanced food safety interventions.<sup>27</sup> Interestingly, 1996-1997 is also when both the decline in GBS reports to VAERS and GBS hospitalizations in the Nationwide Inpatient Sample began. These data raise

intriguing questions about whether GBS among influenza vaccinees may be related to *Campylobacter* infection. Additional research to unravel this possibility may lead to a fuller understanding of the causes of GBS and its possible relationship with influenza vaccine.

**Author Contributions:** Ms Haber had full access to all of the data in the study and takes responsibility for

the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Haber, DeStefano, Iskander, Chen.

**Acquisition of data:** Haber, Weintraub, Chen.

**Analysis and interpretation of data:** Haber, DeStefano, Angulo, Shadomy, Weintraub, Chen.

**Drafting of the manuscript:** Haber, DeStefano, Angulo, Chen.

**Critical revision of the manuscript for important intellectual content:** Haber, DeStefano, Iskander, Shadomy, Weintraub, Chen.

**Statistical analysis:** Haber, Angulo, Shadomy, Weintraub.

**Administrative, technical, or material support:** Haber, Chen.

**Study supervision:** Haber, DeStefano, Iskander, Chen.

**Acknowledgment:** We wish to thank VAERS staff, particularly Marla Sidey-Vener, RN, and Steve Gordon, PharmD, for assistance on GBS reports follow-up; Lu Peng-Jun, MPH, PhD, James Singleton, MS, Barry Sirotkin, MS, and Roseanne English, BS, for helpful suggestions on data analysis; Weigong Zhou, MD, PhD, Amy Dechet, MD, Kristin Holt, DVM, and Tamar Lasky, PhD, for their helpful comments and discussions; and Mary McCauley, MTSC, for insightful editorial comments.

## REFERENCES

- Hughes RA, Rees JH. Clinical and epidemiologic features of Guillain-Barré syndrome. *J Infect Dis*. 1997; 176(suppl 2):S92-S98.
- Schonberger LB, Bergman DJ, Sullivan-Bolyai JZ, et al. Guillain-Barré syndrome following vaccination in the National Influenza Immunization Program, United States, 1976-1977. *Am J Epidemiol*. 1979;110: 105-123.
- Centers for Disease Control and Prevention. Guillain-Barré syndrome—United States. *MMWR Morb Mortal Wkly Rep*. 1976;25:401.
- Langmuir AD, Bregman DJ, Kurland LT, Nathanson N, Victor M. An epidemiologic and clinical evaluation of Guillain-Barré Syndrome reported in association with the administration of swine influenza vaccines. *Am J Epidemiol*. 1984;119:841-879.
- Breman JG, Hayner NS. Guillain-Barré syndrome and its relationship to swine influenza vaccination in Michigan, 1976-1977. *Am J Epidemiol*. 1984;119:880-889.
- Marks JS, Halpin TJ. Guillain-Barré Syndrome in recipients of A/New Jersey influenza vaccine. *JAMA*. 1980;243:2490-2494.
- Safraneck TJ, Lawrence DN, Kurland LT, et al. Reassessment of the association between Guillain-Barré syndrome and receipt of swine influenza vaccination 1976-1977: results of two-states study. *Am J Epidemiol*. 1991;133:940-951.
- Institute of Medicine. *Immunization Safety Review: Influenza Vaccines and Neurological Complications*. Washington, DC: National Academy Press; 2003.
- Hurwitz ES, Schonberger LB, Nelson DB, Holman RC. Guillain-Barré syndrome and the 1978-1979 influenza vaccine. *N Engl J Med*. 1981;304:1557-1561.
- Kaplan JE, Katona P, Hurwitz ES, Schonberger LB. Guillain-Barré syndrome in the United States, 1979-1980 and 1980-1981: lack of an association with influenza vaccination. *JAMA*. 1982;248:698-700.
- Roscelli JD, Bass JW, Pang L. Guillain-Barré syndrome and influenza vaccination in the US Army, 1980-1988. *Am J Epidemiol*. 1991;133:952-955.
- Chen RT, Kent J, Rhodes P, Simon P, Schonberger L. Investigation of a possible association between influenza vaccination and Guillain-Barré syndrome in the United States, 1990-91 [abstract]. *Post Mark Surveill*. 1992;6:5-6.
- Lasky T, Terracciano GJ, Magder L, et al. The Guillain-Barré syndrome and the 1992-93 and 1993-94 influenza vaccines. *N Engl J Med*. 1998;339:1797-1802.
- Chen RT, Rastogi SC, Mullen JR. The Vaccine Adverse Event Reporting System (VAERS). *Vaccine*. 1994; 12:542-550.
- Singleton JA, Lloyd JC, Mootrey GT, et al. An overview of the Vaccine Adverse Event Reporting System (VAERS) as a surveillance system. *Vaccine*. 1999;17: 2908-2917.
- Zhou W, Pool V, Iskander JK, et al. Surveillance for safety after immunization: Vaccine Adverse Event Reporting System (VAERS)—United States, 1991-2001. *MMWR Morb Mortal Wkly Rep*. 2003;52SS-1:1-24.
- Ellenberg SS, Chen R. The complicated task of monitoring vaccine safety. *Public Health Rep*. 1997; 112:10-21.
- Massey JT, Moore TF, Parsons VL, Tadros W. *National Health Interview Survey, 1985-1994: Design and Estimation*. Hyattsville, Md: Public Health Service; 1989. DHHS Publication 89-1384. Vital and Health Statistics, Series 2: Data Evaluation and Methods Research, No. 110.
- United States Government Census Report. 2002. Available at: <http://www.census.gov>. Accessed October 6, 2003.
- Steiner C, Elixhauser E, Schnaier J. The Healthcare Cost and Utilization Project: an overview. *Eff Clin Pract*. 2002;5:143-151.
- O'Mara D, Fukuda K, Singleton JA. Influenza vaccine: ensuring timely and adequate supplies. *Infect Med*. 2003;20:548-554.
- Teutsch SM, Churchill RE, eds. *Principles and Practice of Public Health Surveillance*. 2nd ed. New York, NY: Oxford University Press; 2000.
- Rosenthal S, Chen RT. The reporting sensitivities of two passive surveillance systems for vaccine adverse events. *Am J Public Health*. 1995;85:1706-1709.
- Varricchio F, Iskander J, Destefano F, et al. Understanding vaccine safety information from the Vaccine Adverse Event Reporting System. *Pediatr Infect Dis J*. 2004;23:287-294.
- Rees JH, Soudain SE, Gregson NA, Hughes RAC. *Campylobacter jejuni* infection and Guillain-Barré syndrome. *N Engl J Med*. 1995;333:1374-1379.
- Mishu B, Blaser MJ. Role of infection due to *Campylobacter jejuni* in the initiation of Guillain-Barré syndrome. *Clin Infect Dis*. 1993;17:104-107.
- Centers for Disease Control and Prevention. Preliminary FoodNet data on the incidence of food borne illness: selected sites, United States, 2003. *MMWR Morb Mortal Wkly Rep*. 2004;53:338-343.